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# DYNAMIC SEQUENCES OF STATES IN ENSEMBLES OF MOTOR CORTICAL NEURONS

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## ABSTRACT

A Hidden Markov Model analysis was performed on simultaneously recorded spike-trains in the motor cortex of two monkeys during a delayed center-out task. Preliminary results revealed that the ensemble activity of simultaneously recorded neurons presents a robust sequence of states related to the behavioral task. Most of the time the ensemble of neurons is in a single state that dominates upon the others. Transitions are abrupt and manifest a concomitant change in the firing rate of the neurons. The pattern of states is stable across trials within the same experimental condition.

## KEY WORDS

Motor cortex; parallel spike-trains; Hidden Markov Model; behaving monkey.

## 1. Introduction

Changes in neuronal activity may not necessarily be time-locked to specific sensory or motor events. From trial to trial network processes may occur at different moments and at different speeds. Analysis techniques using averages across trials, such as the peri-stimulus time histogram (PSTH), discard this trial-by-trial variability and, thus, may obscure some features of the neural processes. To account for this, hidden Markov models (HMM) were successfully used in previous studies on simultaneously recorded spike-trains [1,2]. By using this probabilistic method one makes the assumption that network activity goes through a sequence of discrete stable states. Here, states are defined as vectors the components of which are the firing rate of the neurons. Within each state the firing rates are approximatively stationary. Transitions from one state to another are associated with concomitant changes in the firing rate of many neurons. HMM permits to determine the most likely sequence of states that the ensemble of neurons visited within a trial.

Here we provide an example of HMM analysis on simultaneously recorded spike-trains from the motor cortex of a behaving monkey.

## 2. Methods

### *Behavioral task*

Two monkey were trained in a modified delayed center-out task, separating time estimation from movement preparation in two successive delays within each trial [3]. The first delay (time delay), started after the presentation of a non-directional auditory cue (time cue, TC), indicating the duration of both delays, randomly chosen from trial to trial to be either 700ms or 1500ms. At the end of the first delay, the spatial cue (SC) informing about the upcoming movement direction was presented briefly (55ms) and then masked by the onset of all six peripheral targets. The monkey executed the movement after the offset of all targets (GO) at the end of the second delay (preparatory delay). Multi-electrode single unit recordings were made in motor cortex during proficient task execution.

### *Recordings*

After learning the task the monkeys were prepared for multi-electrode recordings in the primary motor cortex of the right hemisphere, contralateral to the trained arm. A multi-electrode, computer-controlled microdrive (MT-EPS, AlphaOmega, Nazareth, Israel) was used to transdurally insert up to 8 micro-electrodes (0.5-1.2M $\Omega$  at 1,000Hz).

### *Hidden Markov Model*

Ultimately, the state of a neural network is determined by the states of all the synapses and all the units of the network. Unfortunately with extra-cellular recordings we cannot access to all these parameters. Only a limited number of simultaneous spike-trains are available. For this reason it is suitable to use a probabilistic approach, such as the HMM, to study the dynamics of an ensemble of neurons.

Under the HMM, a system of  $N$  recorded neurons is assumed to be in one of a predetermined number of states ( $n$ ), which correspond to vectors of the firing rates of the neurons. These vectors are the *observables* of the *hidden*

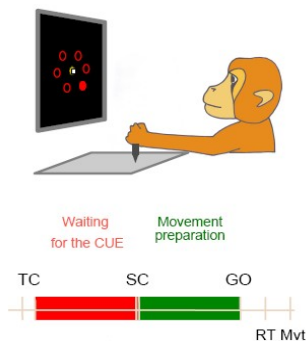
states. The states are *hidden* because they are not directly observed, but are assumed to underlie the recorded spike-trains. In each state, the neurons are assumed to discharge as stationary Poisson processes. We can arrange these vectors in an emission matrix  $E$  defined as  $E_{ij}=r_j^i$  ( $i=1,\dots,N$ ;  $j=1,\dots,n$ ), the instantaneous probability of firing of the neuron  $i$  in the state  $j$ .

Let  $S_t$  be the state at time  $t$ . The transition matrix  $A$  is defined as  $A_{ij}=P(S_{t+1}=j|S_t=i)$ , the probability to move from state  $i$  to state  $j$  at time  $t$ . The transition probabilities,  $A_{ij}$ , are assumed to be independent of time. This means that the system is memoryless: at any time the probability of making a transition from one state to another is constant.

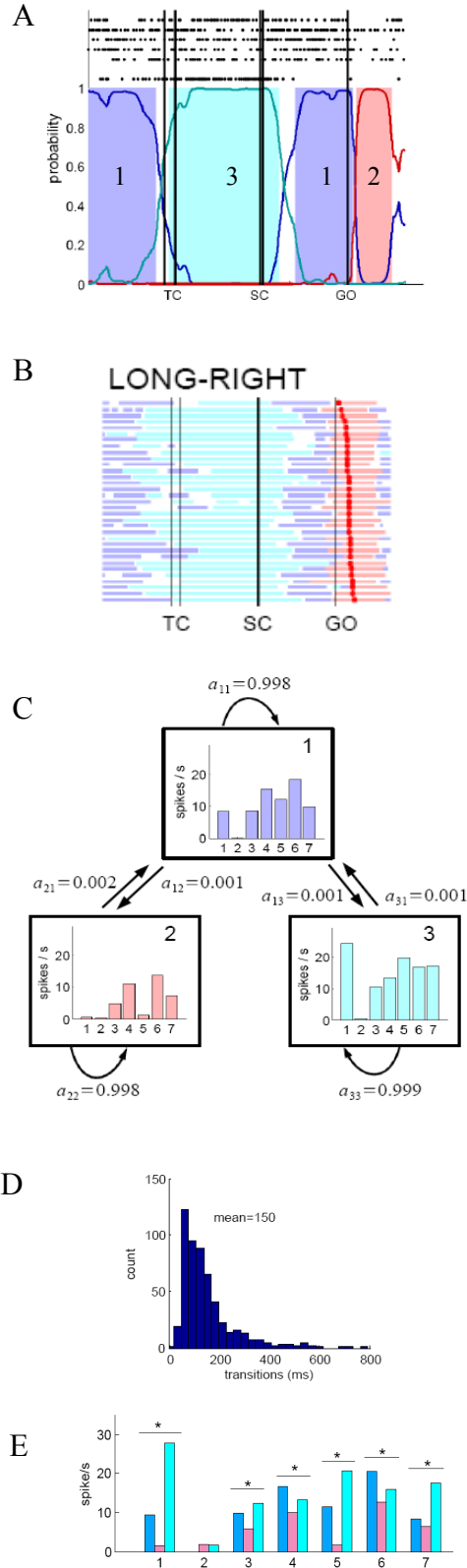
**Training stage.** The model,  $M$ , is fully described by both the emission and transition matrices:  $M=\{E, A\}$ . To choose the model that better explains the data, we estimate the emission and transition matrices that maximize the probability of observing the data given the model. This can be achieved with the Baum-Welch algorithm. The algorithm operates by using random initial values for the emission matrix and transition matrix to calculate the probabilities of the system being in a particular hidden state at each time point, given the observed spike-train for that trial. It then uses these state probabilities to update the emission and transition matrices. Iterations of the algorithm approach a local maximum of the likelihood of observing the data. The algorithm does not guarantee that the maximum reached is global. We then have to run many times (ten) the procedure, with different initial conditions, and choose the highest likelihood output.

**Decoding stage.** Once we found the optimal model parameters, it is possible to determine in each experimental trial the probability of being in each state at any time step (1ms) given the observed spike-trains (see [1] for details):  $P_i=P(S_i|trial\ spike-trains)$ ,  $i=1,\dots,n$ . If this probability is higher than 0.75 we consider that the system is unequivocally in the corresponding state. Periods of uncertainty arise when any of the probabilities  $P_i$  is higher than 0.75.

Note that the number of states,  $n$ , is a parameter fixed by the experimenter.



**Figure 1:** Task. The monkey moved the cursor to the central yellow target (touch) and held it there for 700ms before the temporal cue (TC), a low (700ms delay length) or high (1500ms delay length) frequency tone was presented for 200ms. At the end of the temporal delay (TD), the spatial cue (SC) was briefly presented (a LED at the target location). After 55ms, the SC was masked by the onset of the LEDs at the remaining 5 target locations. At the end of the preparatory delay (PD; same duration as TD), all LEDs went off (GO), and the monkey executed the movement to the cued location.

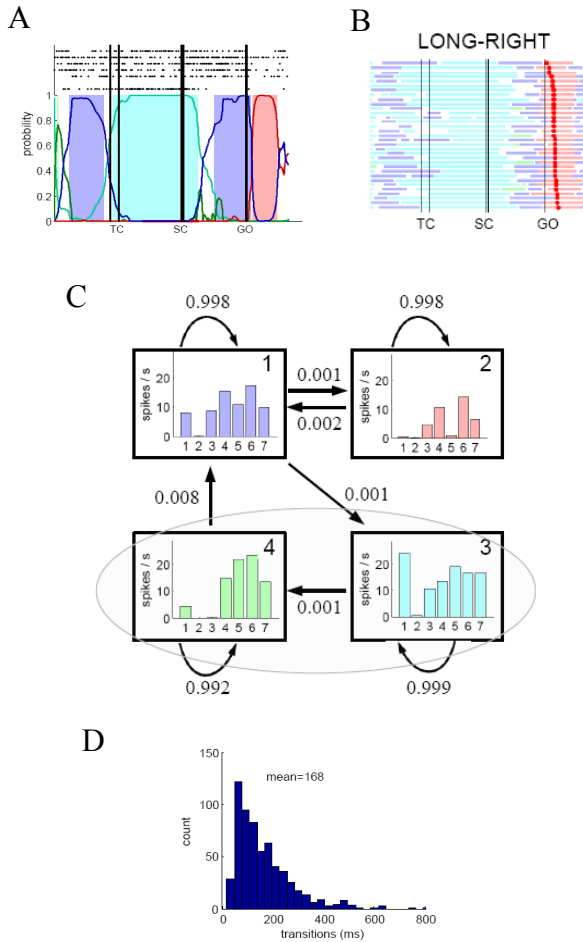


**Figure 2:** A: The 7 horizontal series of dots represent the spike-trains recorded during a representative single long trial. Color lines show the probability of each state through time. Each time the probability is larger than 0.75, the state is indicated by a specific color attributed to each of the 3 states. B: Sequence of states for all trials belonging to the same condition. Periods where a single state dominates ( $p>0.75$ ) are colored. White spaces are periods of uncertainty. Trials are arranged according to increasing reaction times. Red points mark the movement onset. C: States-diagram. The 3 states are represented as histograms specifying the firing rate of each of the 7 neurons and are connected by the transition probabilities (arrows). D: Distribution of transition periods. E: Observed mean firing rate in each state for each neuron. Asterisks mark significant differences ( $P<0.05$ ,  $t$ -test) in firing rates [Recording session #15].

### 3. Results.

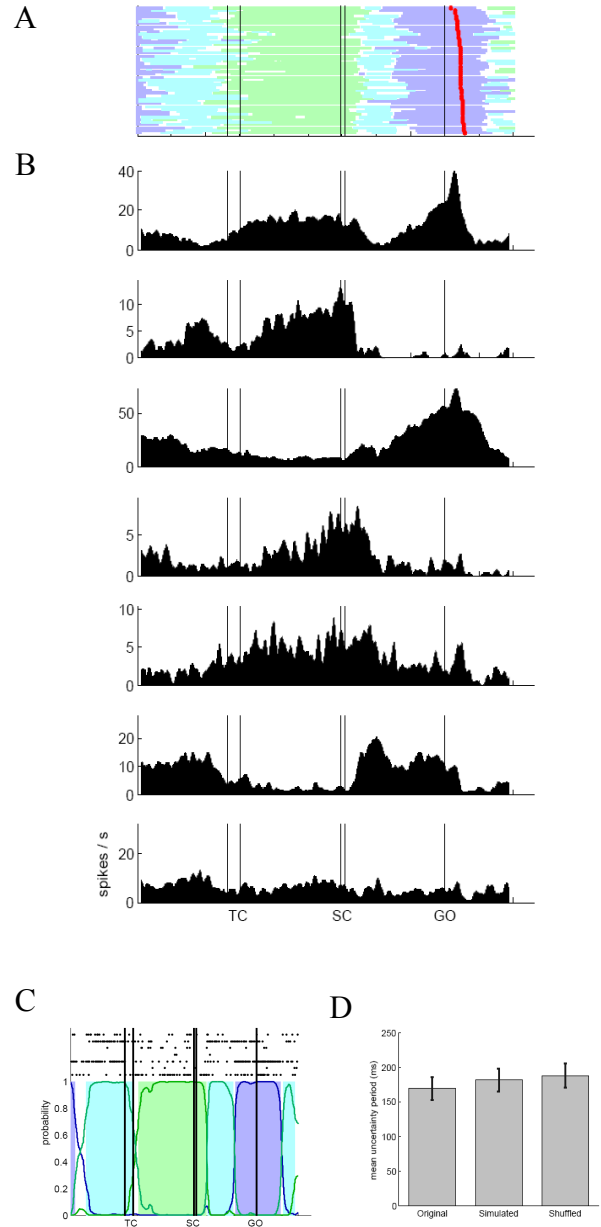
#### *Sequences of discrete states.*

A HMM analysis was performed on the recorded spike-trains. We trained the algorithm with 3 trials randomly chosen from each condition. The optimal model parameters were estimated as described in the *Methods*. The decoding of the data revealed that the activity of an ensemble of simultaneously recorded neurons presents a robust sequence of states related to the behavioral task. Most of the time the ensemble is in one state that dominates upon the others. Figure 2A displays the probability of finding an ensemble of 7 neurons in one of 3 possible states in a single trial. In this trial the sequence of states is clearly related to the task: the ensemble of neurons is in one of the states before TC, during the time delay, during motor preparation, and during movement execution. Transitions are abrupt manifesting a coordinated change in the firing activity of the neurons. As shown in figure 2B, this pattern of states is relatively stable across all trials of the same experimental condition. Interestingly, the times of the transitions are more variable at the beginning of the trial than at the end. This reduction in the variability could be a signature of the commitment to move and is comparable with the reported decrease in spike-count variability during motor preparation [4].



**Figure 3:** 4-states-model. A: State sequence of a particular trial (the same than in figure 1A). B: Sequence of states for all trials belonging to the same condition. C: States-diagram. D: Distribution of transition periods. [Recording session #15].

The states-diagram (figure 2C) reveals that, first, the 3 states are different –6 of the 7 neurons have different firing rates in different states ( $P < 0.05$  by paired  $t$ -test comparing firing rates in different states), as shown in figure 2E. Second, the diagonal elements of the transition matrix ( $A_{ii}$ ) are close to one, meaning that the states are metastable. Third, the states 2 and 3 are disconnected ( $A_{23}=A_{32}=0$ ); to go from state 2 to state 3 and vice versa the system has to pass by state 1.



**Figure 4:** A: Sequence of states for all trials belonging to the same condition. B: Firing rates of the 7 neurons. C: The state probabilities decoded in a trial of the original data. D: Mean transition periods in the original data, the simulated data, and the shuffled data. [Recording session #9].

#### *Addition of states.*

What is the effect of adding another state? To compare the above 3-states-model and a 4-states-model,

we re-ran the algorithm and searched 4 states. As shown in figure 3A-B, the 4<sup>th</sup> state never reaches the criterion of significance: the probability of being in state 4 is always lower than 0.75. The states-diagram (figure 3C) shows that the 3<sup>th</sup> state of the 3-states-model is split in two in the 4-states-model. The 4<sup>th</sup> states perturbs the transitions between state 1 and state 3; as a consequence the transition periods are slightly increased (figures 2D and 3D).

These results suggest that, for this recording session, the activity of the ensemble of neurons is fully described by 3 states.

### *Coherent changes in the ensemble of neurons.*

The HMM analysis on a different session of recordings with 7 neurons is presented in figure 4A. As in the precedent session the system goes through a sequence of discrete states with sharp transitions (figure 4C). To obtain greater insight into what makes the transitions be sharp, we adopted the following strategy. We first calculated the smoothed PSTH for each neuron (figure 4B). Then, we simulated Poisson spike-trains using the PSTHs as the underlying firing rate functions. The same number of trials as in the original data were simulated. In addition, we constructed a shuffled data set: for each experimental condition we randomized the trials of the original data. For instance, “trial” *i* may be constructed with trial 10 of neuron 1, trial 3 of neuron 2, trial 9 of neuron 3, etc. This operation leaves the PSTH profile intact but the spike-trains of the neurons are no more “simultaneous”. Finally, we decoded the two constructed data sets with the transition matrix and the emission matrix obtained with the original data. This procedure allows us to compare two different situations: in the simulated data the spike times are random and the neurons are independent; in the shuffled data the firing rate correlations that are not time-locked are washed.

Figure 4D shows that in the two constructed data sets the transition periods are longer than in the original data. Thus, spike timing and coordinated firing rate changes of the neurons contribute to the sharpness of the transitions.

## **4. Discussion and conclusion.**

The above examples show that the activity of a set of a limited number of neurons from the motor cortex can be effectively described by a sequence of discrete hidden states. The states of the HMM can be associated with volumes in the state-space of the entire network. Within each state the network may be involved in different computations such as expectancy, movement preparation, movement execution, etc. Because the description made by the HMM with only 7 neurons is coarse the states may be degenerated: the corresponding volumes in the state-space may overlap and contain a superposition of other states. This could be the reason why the state 1 in the above example (figure 2) is repeated in two different behavioral contexts: waiting (or expecting) the TC and preparing the movement (or expecting the GO signal).

The robustness of the sequence across many trials of the same condition could be used to align the trials with respect to these states. Many analysis techniques that use

sliding windows (e.g., Fano Factor and Unitary Events) are correct only in the case of stationarity across trials. The results of the HMM allow to align the data according to internal states and to make statistical analyses in which the trial-by-trial variability is taken into account.

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